UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,268	01/20/2004	Huai-Jen Tsai	8961-000009/US	6868

30593 7590 03/08/2007

HARNESS, DICKEY & PIERCE, P.L.C.
P.O. BOX 8910
RESTON, VA 20195

EXAMINER	
BERTOGLIO, VALARIE E	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,268	TSAI, HUAI-JEN	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *5-13 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01/20/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 01/07.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election dated 06/29/2006 has been received. The claims dated 06/29/2006 is entered and under consideration in the instant office action. It is noted that the reply was deemed non-responsive and successive replies were non-compliant under 37 CFR 1.121. However, upon further consideration of the application, it is determined that the claims as amended will not require undue burden to search and examine the multiple promoter species now encompassed. Therefore, the species restriction set forth in the restriction requirement dated 03/29/2006 is withdrawn.

Applicant's election of claims 1-4 (Groups I and II, now rejoined) filed 06/29/2006 without traverse is noted. Applicant has added new claims 5-18. Newly submitted claims 5-13 and 18 are directed to an invention that is independent or distinct from the elected invention as they correspond to Groups III-VI set forth in the restriction requirement dated 03/29/2006. Accordingly, claims 5-13 and 18 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Claims 1-18 are pending and claims 1-4 and 14-17 are under consideration in the instant office action.

Specification

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1 refers to "a fluorescent gene". Genes are not, themselves, fluorescent. However, the products they encode can be. Appropriate correction is required.

Claims 15-17 are objected to because of the following informalities: Claim 15 refers to "fluorescent genes". Genes are not, themselves, fluorescent. However, the products they encode can be. Appropriate correction is required.

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 and 14-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear because of the term "ubiquitous promoter". The metes and bounds of what is encompassed by the term is not clear and is not defined by the specification. The specification gives a number of examples of "ubiquitous promoters", however, it is not clear what other promoters are intended. Claims 3,4, and 14-17 depend from claim 1.

Claim 1 is unclear because of the term "tissue-specific promoter". The metes and bounds of what is encompassed by the term is not clear and is not defined by the specification. The specification gives a number of examples of "tissue promoters", however, it fails to discern whether the term is intended to encompass promoter that driveS gene expression in a single tissue, promoters that drive expression in any tissue or multiple tissues. Claims 2,4, and 14-17 depend from claim 1.

Claim 2 is unclear because it is drawn to a promoter selected from "the group consisting of β-actin...and 5D-rDNA". The group listed is not necessarily a group of promoters but could be interpreted to be a list of genes, cDNAs, or mRNAs etc. The claim should be amended to clearly indicate that the group is a group of promoters.

Claim 3 is unclear because it is drawn to a promoter selected from "a group consisting of α-actin...S-100". The group listed is not necessarily a group of promoters but could be interpreted to be a list of genes, cDNAs, or mRNAs etc. The claim should be amended to clearly indicate that the group is a group of promoters.

Claim 2 is unclear because of the use of the term "elongation-1-a". It is not known if the claim is referring to the promoter known in the art as elongation factor-1-α or some other promoter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1) Claims 1,2, 4 and 15-17 are rejected under 35 U.S.C. 103(a) as being anticipated by Yu *et al.* (November 2002, **Blood**, Vol. 100, Abstract #1698) in view of Flanagan (1987, **Virus Genes**, 1:61-71).

Claim 1 is interpreted as being drawn to a plasmid comprising a ubiquitous promoter operably linked to a first gene encoding a fluorescent protein and a tissue specific promoter operably linked to a second gene encoding a fluorescent protein wherein the promoters are oriented in a divergent orientation with respect to one another such that transcription of the genes are in opposing direction. Claim 2 limits the ubiquitous promoter to a group including elongation-1-α. Claim 4 is drawn to a host cell comprising the plasmid of claim 1.

Yu *et al.* compared a number of methods to introduce multiple reporter genes into cells at a time. Yu *et al.* taught use of vectors to efficiently transduce multiple genes into cells by placing an IRES between the coding regions for the two genes. Yu *et al.* found, however, that the upstream gene can greatly cause a decrease in expression of the gene downstream of the IRES. Yu et al. found that making fusion genes was also inefficient. However, Yu *et al* report that use of separate, unique promoters, to drive expression of each desired reporter gene resulted in expression of both reporter genes. Yu *et al.* taught use of constitutive promoters including EF-1α (claim 2) and CMV operably linked to GFP and RFP, respectively (claims 15-17). Yu *et al.* used tissue specific promoters as well including MHC-II-specific HLA-Drα, in combination with a constitutive promoter. Yu *et al* taught cells comprising the recombinant plasmid (claim 4). Thus, Yu *et al*, taught a plasmid comprising a first tissue-specific promoter operably linked to a first

gene encoding a fluorescent protein and a second, constitutive promoter operably linked to a second gene encoding a different fluorescent protein.

Yu did not discuss the respective orientations of each transgene within the vector.

However, Flanagan taught a recombinant plasmid, pCAL, similar in generic composition to that of Yu *et al.*, comprising two different reporter genes, CAT and β-gal, in opposing direction, driven by two different promoters (see Figure 1). Flanagan taught use of various HSV-1 promoters as the plasmid was used for the purpose of comparing the activity of different promoters by comparing the resulting reporter gene expression. Flanagan taught that divergent orientation of the promoters minimized any interference between the promoters (pages 67-70).

One of skill in the art at the time of filing would have been motivated to combine the teachings of Yu et al. relating to a plasmid comprising two independent genes wherein each gene comprises a gene encoding a fluorescent protein operably linked to different promoters, with one promoter being a constitutive promoter and the other being a tissue-specific promoter, with those of Flanagan teaching that divergent orientation of two promoters within a single plasmid construct reduces promoter interference. One would be motivated to make such a combination such that the activity observed from each promoter is true and characteristic of that promoter and not influenced by the presence of other, unrelated promoter elements.

One of skill in the art would have a reasonable expectation of success in combining the above teachings as the molecular tool and technology was well known, routine and available at the time of filing.

Claims 3 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu *et al.* in view of Flanagan *et al.* as applied to claims 1,2, 4 and 15-17 above, and further in view of Ju et al (1999, Developmental Genetics, 25:158-167) or Higashijima (1997, Developmental Biology, 192:289-299).

As set forth above, Yu *et al.*. and Flanagan *et al.*, together, taught a plasmid comprising a first tissue-specific promoter operably linked to a first gene encoding a fluorescent protein and a second, constitutive promoter operably linked to a second gene encoding a different fluorescent protein, with the promoters being in divergent orientation. Neither Yu *et al.* nor Flanagan *et al.* taught use of a muscle or skin-specific promoter.

However, Ju *et al.* taught the isolation and use of both a skin-specific (cytokeratin) and a muscle specific (muscle creatine kinase) promoter to drive GFP expression in cells. Furthermore, Higashijima taught isolation of the muscle-specific α-actin promoter (claim 3)

It would have been obvious at the time of filing to substitute the tissue-specific promoters used by Yu *et al.* with one of those taught by Ju *et al.* to drive specific fluorescent reporter gene expression in either skin or muscle. One of skill in the art would have been motivated to use the skin and/or muscle-specific promoters in place of the tissue-specific promoters of Yu *et al.* because, as taught by Ju *et al.* (see Discussion, Ju *et al.*) the green fluorescent labeled cells can be used to monitor specific cell lineages during development as well as be specifically visualized for numerous other purposes. Visualizing in vivo, say GFP cells, in a ubiquitously red fluorescent animal, would allow visualization of tissue specific expression while positively identifying cells as having a transgene based on red fluorescence, especially in a chimeric or mosaic expressing animal.

One of skill in the art would have a reasonable expectation of success in combining the above teachings as the molecular tool and technology was well-known, routine and available at the time of filing.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Thavathiru and Das [Biotechniques, 31:528-532, 2001] is a mere example of the many examples in the art using a dual reporter system with either fluorescent or chemiluminescent reporters, differing reporters each operably linked to either a constitutive or a tissue-specific promoter, the constitutive promoter construct providing an internal control and the tissue-specific or cell-specific promoter being an experimental. Thavathiru and Das is not relied upon in the instant office action because relevant art teaching the constructs in a single plasmid is of record. However, it is important to note the routine and important nature of having both a constitutive promoter as an internal control for comparison in assaying variables of an experimental promoter.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Valarie Bertoglio
Examiner
Art Unit 1632